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Published in:
Taurine 10

DOI:
10.1007/978-94-024-1079-2_45

Publication date:
2017

Document Version
Peer reviewed version

The Interaction of Hypotaurine and Other Sulfinates with Reactive Oxygen and Nitrogen Species: A Survey of Reaction Mechanisms

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Abstract Considerable strides have been made in understanding the oxidative mechanisms involved in the final steps of the cysteine pathway leading to taurine. The oxidation of sulfinates, hypotaurine and cysteine sulfinic acid, to the respective sulfonates, taurine and cysteic acid, has never been associated with any specific enzyme. Conversely, there is strong evidence that in vivo formation of taurine and cysteic acid is the result of sulfinate interaction with a variety of biologically relevant oxidants. In the last decade, many experiments have been performed to understand whether peroxynitrite, nitrogen dioxide and carbonate radical anion could be included in the biologically relevant reactive species capable of oxidizing sulfinates. Thanks to this work, it has been possible to highlight two possible reaction mechanisms (direct and indirect reaction) of sulfinates with reactive oxygen and nitrogen species.

The sulfinates oxidation, mediated by peroxynitrite, is an example of both reaction mechanisms: through a two-electron – direct – reaction with peroxynitrite or through a one-electron – indirect – transfer reaction. In the indirect mechanism, the peroxynitrite homolysis releases hydroxyl and nitrogen dioxide radical and in addition the degradation of short-lived adduct formed by peroxynitrite and CO_2 can generate carbonate radical anion. The reaction of hypotaurine and cysteine sulfinic acid with peroxynitrite-

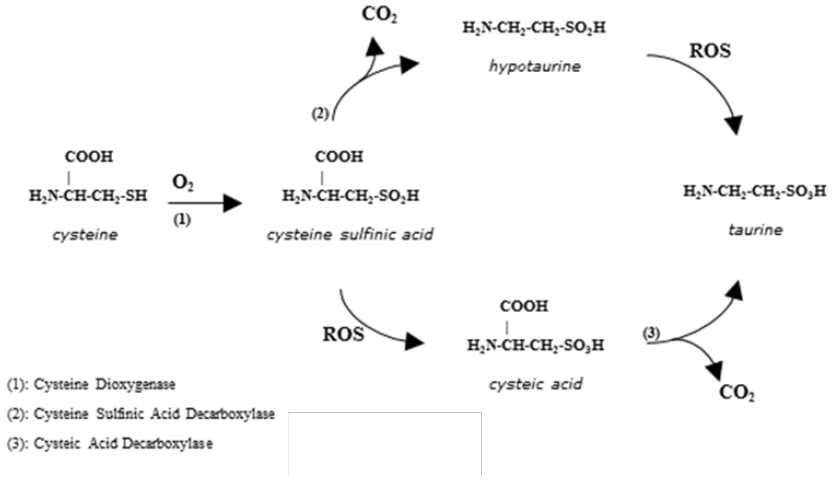
derived radicals is accompanied by extensive oxygen uptake with the generation of transient intermediates, which can begin a reaction by an oxygen-dependent mechanism with the sulfonates, taurine, and cysteic acid as final products. Due to pulse radiolysis studies, it has been shown that transient sulfonyl radicals ($RSO_2^{\bullet}$) have been produced during the oxidation of both sulfinates by one-electron transfer reaction.
The purpose is to analyze all the aspects of the reactive mechanism in the sulfinic group oxidation of hypotaurine and cysteine sulfinic acid through the results obtained from our laboratory in recent years.

Abbreviations: RSO_2^-, sulfinates; $RSO_2^{\bullet}$, sulfonyl radicals; RSO_3^-, sulfonates; $RSO_2OO^{\bullet}$, sulfonyl-peroxyl radicals; HTAU, hypotaurine; CSA, cysteine sulfinic acid; TAU, taurine; CA, cysteic acid; $ONOO^-$, peroxynitrite; $CO_3^{\bullet-}$, carbonate anion radical; $^{\bullet}NO_2$, nitrogen dioxide; $^{\bullet}NO$, nitric oxide

1.1 INTRODUCTION

Hypotaurine (HTAU) and cysteine sulfinic acid (CSA) are the last two metabolic intermediates in the production of taurine in the mammalian cysteine pathway. This pathway is dependent upon three specific enzymes as well as a variety of biologically relevant oxidizing agents (scheme 1) (Huxtable 1992; Stipanuk and Ueki 2011; Ricci et al 1978; Fontana et al 2005; Fellman et al., 1987; Aruoma et al., 1988; Pecci et 1999; Baseggio Conrado et al 2014). It is well known that cysteine dioxygenase is the first enzyme involved in this pathway and its activity leads to CSA. With the addition of molecular oxygen to the cysteine, to its sulfur atom, there is a conversion to the sulfinic acid from the thiol. (Stipanuk and Ueki 2011). At this point, the pathway can go in one of two directions both of which lead to taurine (TAU). In the first, a decarboxylation occurs and HTAU is produced due to the activity of CSA decarboxylase, and the sulfinic group of HTAU is subsequently oxidized to the sulfonic group of TAU. CSA can also undergo oxidation to produce cysteic acid (CA) and, through subsequent decarboxylation, forms TAU (Scheme 1) (Huxtable 1992; Stipanuk and Ueki 2011). This crucial point, the sulfinic group oxidation to the respective sulfonic group, has never been associated with any specific enzyme (Wright et al. 1986; Huxtable 1992). Conversely, evidences that in vivo formation of TAU and CA is the result of sulfinate (RSO_2^-) interaction with a variety of biologically relevant oxidizing agents, are strong

(Ricci et al. 1978; Fellman et al. 1987; Aruoma et al. 1988; Pecci et al. 1999; Fontana et al. 2005; Baseggio Conrado et al. 2014).



Scheme 1. Hypotaurine and cysteine sulfinic acid as intermediates in the mammalian pathway leading from cysteine to taurine

Even though reactive oxygen species (ROS) are known to be capable of oxidizing the sulfinic group of HTAU and CSA, only hydroxyl radicals ($^{\bullet}OH$) and singlet oxygen have shown high direct reactivity leading to TAU formation (Pecci et al. 1999 and 2000; Arouma et al. 1988). This is in spite of low direct reactivity between hydrogen peroxide (H_2O_2), superoxide anion ($O_2^{\bullet-}$) and RSO_2^- (Aruoma et al. 1998).
The oxidation of both HTAU and CSA to TAU and CA, respectively, can be also mediated by peroxynitrite ($ONOO^-$) (Fontana et al. 2005 and 2006). The sulfinate oxidation mediated by $ONOO^-$ is an example of both direct and indirect reactions: via a two-electron mechanism (direct reaction) with $ONOO^-$ or by a one-electron transfer mechanism (indirect reaction). In the indirect mechanism, the $ONOO^-$ homolysis releases hydroxyl ($^{\bullet}OH$) and nitrogen dioxide ($^{\bullet}NO_2$) radical and in addition the degradation of short-lived adduct formed by $ONOO^-$ and CO_2 can generate carbonate radical anion ($CO_3^{\bullet-}$) (Fontana et al. 2005 and 2008). Two previous studies, using the peroxidase activity of Cu-Zn superoxide dismutase and horseradish peroxidase, carried out from our group have demonstrated the importance of both carbonate anion and nitrogen dioxide radicals in the oxidation of HTAU (Baseggio Conrado et al. 2014 and 2015). The reaction of HTAU and CSA with peroxynitrite-derived radicals is accompanied by extensive oxygen uptake suggesting the generation of transient sulfonyl

radicals ($RSO_2^{\bullet}$), which can begin a reaction by an oxygen-dependent mechanism with the sulfonates (RSO_3^-), TAU and CA, as final products (Fontana et al. 2005 and 2006). Pulse radiolysis studies showed that transient sulfonyl radicals ($RSO_2^{\bullet}$) have been produced during the oxidation of both sulfinates by one-electron transfer reaction (Baseggio Conrado et al. 2014). The findings that HTAU and CSA efficiently react with hydroxyl radical, singlet oxygen as well as $CO_3^{\bullet-}$ and $^{\bullet}NO_2$ provided further support for the proposed role of these compounds as antioxidants and free radical-trapping agents in vivo (Green et al. 1991; Tadolini et al. 1995; Fontana et al. 2004). Of note, in all studies performed on the antioxidant activity of both RSO_2^-, the scavenger effect of CSA on different targets, such as tyrosine dimerization, is higher than that exerted by HTAU, which can be explained considering the CSA-derived sulfonyl radicals. These transient radicals can undergo degradation to sulfite, a secondary product with an efficient protective effect against oxidative reactions. Instead, the $RSO_2^{\bullet}$ derived from the HTAU oxidation seems to have a reduced tendency to decay.

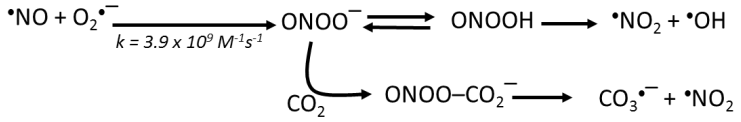
The mechanisms involved in the interaction of the reactive oxygen (ROS) and nitrogen species (RNS) with RSO_2^-, HTAU and CSA, have only recently been investigated in depth (Fontana et al. 2005; Baseggio Conrado et al. 2014). In particular, starting from the findings of Cavallini and coworkers (Ricci et al. 1978; Pecci et al. 1999 and 2000) and subsequently, through experiments performed to understand whether peroxynitrite could be included in the biologically relevant reactive species capable of oxidizing RSO_2^-, it has been possible to highlight the reaction pathway mechanism of RSO_2^- leading to RSO_3^- (Fontana et al 2005 and 2006).

1.2 Sulfinic group oxidation by one-electron pathway (indirect reaction)

In recent years, through three different oxidants – $ONOO^-$, $^{\bullet}NO_2$ and $CO_3^{\bullet-}$ – that were tested for inclusion as oxidant agents capable of oxidizing the sulfinic group of RSO_2^-, it has been possible to define the indirect one-electron pathway in the reaction from RSO_2^-, HTAU or CSA, to RSO_3^-, TAU or CA (Baseggio Conrado et al. 2014; Fontana et al. 2005). The extensive $ONOO^-$ studies were due to both its strong oxidizing and nitrating effect on substrates. It has been suggested that the damage in cellular and tissue in neurodegenerative disorders as well as in inflammatory and autoimmune disease can be related to the oxidizing and nitrating effect of $ONOO^-$ that acts as a reactive toxic species (Stewart and Heales 2003; Koppenol et al. 1992; Pryor and Squadrito 1995; Huie and Padmaja 1993;

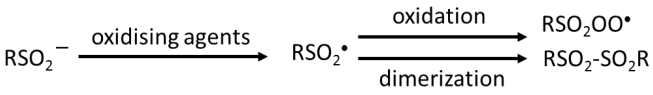
Eiserich et al. 1998;). In vivo, nitric oxide ($^{\bullet}NO$) and $O_2^{\bullet-}$ can react through a diffusion-controlled reaction and produce $ONOO^-$ (scheme 2) (Beckman et al. 1990; Pryor and Squadrito 1995). It has been described that $ONOO^-$ could be present with its conjugate acid (ONOOH, $pK_a = 6.8$) which decays rapidly ($t_{1/2} < 1$ s). ONOOH homolysis can generate two radicals, $^{\bullet}OH$) and $^{\bullet}NO_2$, capable of oxidizing through an indirect one-electron reaction other target substrates (Radi et al. 2001). Moreover, the decomposition of peroxynitrite-CO_2 adducts, produced under physiological conditions by peroxynitrite predominant reaction with CO_2, can generate $CO_3^{\bullet-}$ and $^{\bullet}NO_2$ (Scheme 2) (Lymar and Hurst 1998; Meli et al. 2002; Augusto et al. 2002). It has been shown that $CO_3^{\bullet-}$ and $^{\bullet}NO_2$ stimulate the oxidation, peroxidation, and nitration of several biological targets (Beckman et al. 1990). Furthermore, Bonini and collaborators have suggested that the $ONOO^-$ production and peroxidase activity of superoxide dismutase (SOD) can play a key role as mediator in the oxidative damage (Bonini et al. 2004a; Bonini et al. 2004b).

$CO_3^{\bullet-}$ is a strong acid ($pK_a < 0$) that through a one-electron mechanism ($E° = 1.5$ V) can oxidize many biological targets that consequently produces radicals (Augusto et al. 2002; Bonini and Augusto 2001). $^{\bullet}NO_2$ is a neutral radical and shows a greater selectivity towards biomolecules, compared to $CO_3^{\bullet-}$. $^{\bullet}NO_2$ can mediate oxidation and nitration of various substrates and it can be generated by many physiological processes, such as $^{\bullet}NO$ autoxidation, homolysis of $ONOO^-$ or its addition to CO_2 (Farrel et al. 1992; Torre et al. 1996; Brennan et al. 2002). The relevance of these two radicals in the oxidation of RSO_2^- has been analysed through the peroxidase activity of two different enzymes, the Cu-Zn SOD and horseradish peroxidase (Baseggio Conrado et al. 2014 and 2015). In particular, we have shown that diffusible $CO_3^{\bullet-}$, produced by the SOD/H_2O_2 system with bicarbonate, is involved in sulfinate oxidation suggesting the generation of transient intermediates in the oxidative step of RSO_2^- to RSO_3^- (Baseggio Conrado et al. 2014).



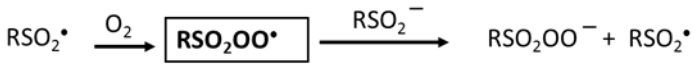
Scheme 2. Formation and fate of peroxynitrite at physiological pH

1.3 Sulfonyl radical ($RSO_2^{\bullet}$)/sulfonyl-peroxyl radical ($RSO_2OO^{\bullet}$) as transient intermediates in the one-electron pathway of sulfinic group oxidation



Scheme 3. One-electron pathway of sulfinate oxidation

In the indirect one-electron pathway of the RSO_2^- oxidation, the first step is the reaction between RSO_2^- and biological oxidizing agents, such as carbonate radical anion, hydroxyl radical and nitrogen dioxide, and is accompanied by the formation of $RSO_2^{\bullet}$ (Aruoma et al. 1988; Sehested and Holcman, 1996; Fontana et al 2005 and 2008; Baseggio Conrado et al. 2014 and 2015). Acting as a strong oxidizing species, $RSO_2^{\bullet}$ can produce the sulfonyl-peroxyl radical ($RSO_2OO^{\bullet}$) when oxygen is present (Scheme 3) (Sevilla et al. 1990).
The above fate for the $RSO_2^{\bullet}$ is not the only one, actually, $RSO_2^{\bullet}$ can dimerize and produce the disulfone derivative (RSO_2-SO_2R) (Fellman et al. 1987; Ricci et al. 1978; Green and Fellman 1994).
Pulse radiolysis studies carried out by our group, used to evaluate the one-electron oxidation rate between RSO_2^-, HTAU and CSA, with $^{\bullet}OH$, $CO_3^{\bullet-}$, and $^{\bullet}NO_2$, has supported the evidence of the production of $RSO_2^{\bullet}$ (Baseggio Conrado et al. 2014). We have observed that during the reaction between HTAU or CSA with $CO_3^{\bullet-}$ at pH 7.4 maximum absorption spectra around 320 nm (within a region of 300-350 nm), and at 600 nm was also observed a decay of $CO_3^{\bullet-}$ absorption spectra. (Baseggio Conrado et al. 2014). Taking into account that Sehested and Holcman (1996) observed during the oxidation of methansulfinic acid by $^{\bullet}OH$ a sulfonyl radical (maximum optical absorption spectra around 325 nm), the spectra obtained in the reaction between RSO_2^- and oxidizing agents, such as $^{\bullet}OH$, $CO_3^{\bullet-}$ and $^{\bullet}NO_2$, can be attributed to $RSO_2^{\bullet}$ as a transient intermediate.

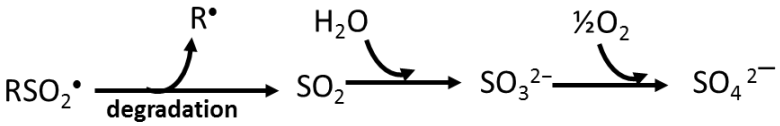


Scheme 4. Formation and fate of sulfonyl-peroxyl radical

In the $ONOO^-$ experiments, the oxidation of RSO_2^-, HTAU and CSA has been shown to be associated with an extensive oxygen uptake (Fontana et al. 2005 and 2006). The high O_2 consumption observed is related to the strong oxidizing activity of $RSO_2^{\bullet}$ which reacts with oxygen producing the

sulfonyl-peroxyl radical ($RSO_2OO^{\bullet}$). $RSO_2OO^{\bullet}$ is an intermediate in this mechanism and also a highly reactive species that can react with excess RSO_2^- and produce peroxysulfonate (RSO_2OO^-) (Scheme 4) (Sevilla et al. 1990).

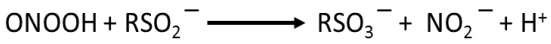
1.4 Different fates of HTAU- and CSA-derived sulfonyl radicals generated by one-electron sulfinate oxidation



Scheme 5. Decomposition pathway of sulfonyl radical to sulfite/sulfate

In all experiments performed to detect the yield in the production of RSO_3^-, TAU and CA, from RSO_2^-, HTAU and CSA, a different behaviour has always been reported between the HTAU- and CSA-derived sulfonyl radical (Pecci et al. 2000; Fontana et al. 2005 and 2006; Baseggio Conrado et al. 2014 and 2015). It has been shown that only a fraction of the depleted CSA was oxidized to CA with a yield of around 17%, compared with the almost total oxidation of HTAU in TAU (Baseggio Conrado et al. 2014). Sulfonyl radical derived by CSA has a high tendency to degrade to acetaldehyde and concurrently producing ammonia, CO_2, and sulfite (Harman et al. 1984; Pecci et al. 2000). In detail, CSA-derived sulfonyl radicals partly undergo decomposition, producing sulfur dioxide (SO_2) and a highly carbon-centred radical ($R^{\bullet}$) which can react with O_2 and further degrade to end products, such as ammonia or CO_2 (Scheme 5) (Pecci et al. 2000). In contrast, HTAU-derived sulfonyl and sulfonyl-peroxyl radicals are more stable. It is likely that these highly reactive radicals could also promote the oxidation of suitable target molecules (Fontana et al. 2008).

1.5 Two-electron mechanism of sulfinic group oxidation (direct reaction)

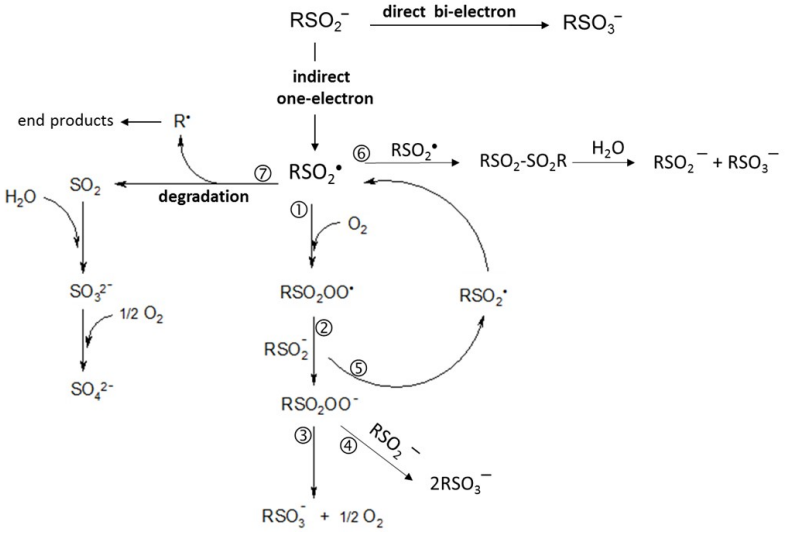


Scheme 6. Two-electron mechanism of sulfinate oxidation

In the pathway leading from RSO_2^- to RSO_3^-, a route in addition to the one-electron mechanism can occur without any oxygen consumption. This route is a two-electron mechanism that can directly produce the RSO_3^- (Scheme 6) (Fontana et al. 2005 and 2006).
In this reaction, oxygen is transferred directly from $ONOO^-$ to RSO_2^- with the production of RSO_3^- and nitrite in stoichiometric amounts. According to kinetic experiments, the direct reaction between $ONOO^-$ and HTAU or CSA appears to be a second-order rate with, respectively, 77.4 and 76.4 $M^{-1}s^{-1}$ constant. Moreover, ONOOH can be considered the reactant in the direct oxidative pathway as a correlation between k_{app} build-up and pH decrease has been observed (Fontana et al. 2005).

1.6 Conclusion

The oxidation of sulfinates, HTAU and CSA, by reactive oxygen and nitrogen species to form sulfonates, TAU and CA, may occur either through one- or two-electron pathways as shown in scheme 7.



Scheme 7. One and two-electron pathway for the oxidative reactions of sulfinates

To briefly overview the one-electron mechanism: the reaction between sulfinates (RSO_2^-) and one-electron oxidants, such as $ONOO^-$, $CO_3^{\bullet-}$ and $^{\bullet}NO_2$, is accompanied by the generation of intermediate sulfonyl radicals ($RSO_2^{\bullet}$). Acting as a strong oxidizing species, $RSO_2^{\bullet}$ can produce the sul-

fonyl-peroxyl radical ($RSO_2OO^{\bullet}$) when oxygen is present (① in Scheme 7) (Sevilla et al. 1990; Flyunt et al. 2001). $RSO_2OO^{\bullet}$ is an intermediate in this mechanism and also a highly reactive species that can react with excess RSO_2^- and produce peroxysulfonate (RSO_2OO^-) (② in Scheme 7). Subsequently, the RSO_2OO^- formed decomposes to yield sulfonate (RSO_3^-) and molecular oxygen or oxidizes the excess RSO_2^- to RSO_3^- (③ and ④ in Scheme 7).

Moreover, $RSO_2^{\bullet}$ can either proceed through other three routes. It may initiate an oxygen-dependent radical chain propagation with a possible amplification of the oxidative mechanism (⑤ in scheme 7) (Sevilla et al. 1990; Flyunt et al. 2001) or it can dimerize to form disulfone derivative (RSO_2–SO_2R), that subsequently hydrolyzes to yield RSO_3^- (⑥ in Scheme 7) (Ricci et al. 1978; Fellman et al. 1987; Green and Fellman 1994). The dimerization route does not require oxygen and can be operative in systems when low oxygen uptake is observed or in anaerobiosis (Ricci et al. 1978; Pecci et al. 1999; Baseggio Conrado et al. 2015).

The last possible route in the indirect pathway is the decomposition of $RSO_2^{\bullet}$. As reported above, especially CSA-derived sulfonyl radicals can partly undergo degradation with production of sulfite (⑦ in scheme 7) (Harman et al. 1984; Pecci et al. 2000).

In the two-electron process, the direct transfer of oxygen from the oxidant, such as $ONOO^-$, to RSO_2^- generates RSO_3^- without any oxygen consumption. Which pathway occurs, between the one or two-electron mechanisms, depends mainly on RSO_2^- concentration. In fact, in the $ONOO^-$-mediated oxidation, it has been shown that at low RSO_2^- concentration, $RSO_2^{\bullet}$ formation is associated with high oxygen uptake via the one-electron mechanism. On the contrary, at high RSO_2^- concentration, the second-order reaction (between RSO_2^- and $ONOO^-$) becomes more significant, producing a decrease in the oxygen consumption and consequently the direct oxidation of RSO_2^- without the formation of $RSO_2^{\bullet}$ predominates (Fontana et al. 2005 and 2006).

It is noteworthy that the sulfonyl and sulfonyl-peroxyl radicals produced in this mechanism are highly reactive oxidizing agents and could promote oxidative reactions (Pecci et al. 2003; Fontana et al. 2008; Baseggio Conrado et al. 2014). Looking forwards, it would be interesting to investigate the pathophysiological role of sulfonyl or sulfonyl-peroxyl radicals, particularly considering the increased significance of reactive sulfur species (RSS) in cellular oxidative stress. (Schöneich et al. 1992; Giles and Jacob 2002; Jacob 2012).

As outlined in this review, many questions on the oxidative mechanism of sulfinates to sulfonates have been addressed, however, the actual biologi-

cal relevance and the pathophysiological role of generated reactive intermediates deserve to be further investigated.

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